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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,921	09/24/2001	Didier Raoult		3015

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EXAMINER	
BASKAR, PADMAVATHI	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 12/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,921	RAOULT ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,10,11,15,25 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,11,15,25 and 29-31* is/are rejected.

7)☒ Claim(s) *3, 10, 32 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *11/21/05*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment

1. Applicant's amendment filed on 9/9/05 is acknowledged.

Status of Claims

2. Claims 2, 6-9, 12-14, 16-24 and 26-28 are canceled.

New claims 30-33 have been added.

Claims 1, 3,4,11, 15, and 29 have been amended.

Claims 1, 3-5, 10, 11, 15, 25, 29 and 30-33 are pending and are under examination in the application.

Claim Rejections - 35 USC 102 maintained

3. The rejection of claims 1-5 and 10 under 35 U.S.C. 102(b) as being anticipated by Schoedon et al 1997 is maintained as set forth in the previous office action.

The Claims are drawn to a culture comprising a bacterium responsible for Whipple's disease, isolated and established in culture such that the bacterium reproducibly multiplies over time, wherein the bacterium is *Tropheryma whippelii,* said bacterium isolated and obtained from a culture of human fibroblasts after at least 2 months of incubation in a culture medium based on MEM.

Schoedon et al disclose a culture comprising isolation of *Tropheryma whippelii* bacterium (see Journal Infectious diseases, 176; 672-677) responsible for Whipple's disease (see abstract) from biopsy material obtained from a patient. The bacterium is cultured in medium containing (see figure1) deactivated mononuclear phagocytes (see page 673, right column, under inoculation of cultures) and this bacteria has been expanded in a large volume of cells SigM5 in growth medium (see page 673, right column) thus read on claims 1 and 2. Since isolated bacteria is routinely used as an antigen in the art, the bacteria isolated from PMNC read on claims 3-5 and 10 because these claims do not distinguish the bacterium from the prior art as the art disclosed the same *Tropheryma whippelii.* The prior art anticipated the claimed invention. Recitation of "established in culture such that the bacterium reproducibly multiplies over time" is viewed as a process limitation. Where a claim is rejected over a prior art product that is identical, although produced by a different process, the burden is upon the applicants to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Thorpe*, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985). *In re Marosi*, 218 U.S.P.Q. 289, 293-293 (C.A.F.C. 1983). *In re Best*, 195 U.S.P.Q. 430, 433 (C.C.P.A. 1977). *In re Brown*, 173 U.S.P.Q. 685, 688 (C.C.P.A. 1972). Further, the structure of the bacterium obtained by the prior art and the claimed bacterium are the same because both of them are *Tropheryma whippelii.*

In claim 2 " bacterium obtained from a culture of human fibroblasts after at least 2 months of incubation in a culture medium based on MEM" is also considered as a process limitation. The product of the prior art and the claimed product are the same because the claimed product produced in human fibroblast does not distinguish the product of the prior art in the absence of other structural characteristics. The patentability is based on the product itself. The patentability of a product does not depend upon its process. If the product of the claim is the same as the product of the prior art, the claim is unpatentable even though the product was made by a different process. Where a product claim is rejected over a prior art product that appears to be identical, although produced by a different process, the burden is upon the applicants to provide evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Thorpe*, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985). *In re Marosi*, 218 U.S.P.Q. 289, 293-293 (C.A.F.C. 1983). *In re Best*, 195 U.S.P.Q. 430, 433 (C.C.P.A. 1977). *In re Brown*, 173 U.S.P.Q. 685, 688 (C.C.P.A. 1972). The prior art anticipated the claimed invention.

4. The rejection of claims 1, 4-5 ,30, and 31 under 35 U.S.C. 102(b) as being anticipated by Muller et al 1999 GASTROENTEROLOGY. Vol, 116, No. 4. Part 2, Abstract 910, 1999. (Abstract only) is maintained as set forth in the previous office action.

The prior art discloses *T.Whippelii* replicate in IL4 treated monocytic U937 cell line (see abstract) and thus the bacteria multiply over the time. Since isolated bacteria is routinely used as an antigen in the art, the bacteria isolated from PMNC read on claims 3-5 and 10 because these claims do not distinguish the bacterium from the prior art as the art disclosed the same *Tropheryma whippelii.* The prior art anticipated the claimed invention. The prior art anticipated the claimed invention.

5. The rejection of claims 1, 4-5, 30, and 31 under 35 U.S.C. 102(b) as being anticipated by Drancourt 1999 Presse Medicale, Vol. 2: No. 8, February 27. 1 999, pp. 435-439 (See translated article) is maintained as set forth in the previous office action

The prior art discloses *T.Whippelii* is isolated from two heart valves sampled from two patients, deactivated by a combination of dexamethasone, interleukin-4 (1L-4) and IL10 (see Table 1) and bacteria was cultivated or propagated in human cell line, monoblast SigM5 (see page 8, bottom of the page) and thus the bacteria multiply over the time. This cell line grows continuously in cell culture as SigM5 is an immortalized cell line and it is not primary human monocytes and thus meets the limitations of claim 30 and 31. Since isolated bacteria is routinely used as an antigen in the art, the bacteria isolated and propagated read on claims 3-5 and 10 because these claims do not distinguish the bacterium from the prior art as the art disclosed the same *Tropheryma whippelii.* The prior art anticipated the claimed invention.

Claim Rejections - 35 USC § 103 maintained

6. The rejection of claims 11,15, 25 and 29 under 35 U.S.C. 103(a) as being unpatentable over Muller et al 1999 Gastroenterology. Vol, 116, No. 4. Part 2, Abstract 910,1999. or Muller 1999 Presse Medicale, Vol. 2: No. 8, February 27. 1999, pp. 435-439 in view of Harlow and Lane 1986, Cold Spring Harbor Laboratory 1988, (chapter 14) is maintained as set forth in the previous office action.

Muller et al or 1999 or Drancourt 1999 as stated above teach an isolated *Tropheryma whippelii* bacterium or antigen associated with Whipple's disease. However, the prior art does not teach a method of diagnosis comprising contacting the serum or any other biological fluid with bacteria or antigen on a solid support and detecting the immunological reaction.

Harlow and Lane teach several immunoassays for detecting antibodies in a sample using antigen assays. These immunoassays are listed in Table 14.1 including the method for detecting antibody (see page 560-561, 563) using antigen. The method comprises contacting the antigen on a solid support with the test solution (i.e., serum, biological fluid etc) and detecting the antibody and antigen reaction (immunological reaction) using labeled secondary reagent.

An artisan of ordinary skill would have been motivated to use *Tropheryma whippelii* bacterium or antigen in an immunoassay for the in vitro diagnosis of diseases associated with infections caused by *Tropheryma whippelii* because Drancourt 1999 clearly suggests that isolation of *Tropheryma whippelii* opens the way to the production of antigen for immunological diagnosis (see page 9 of Drancourt 1999). Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to *Tropheryma whippelii* bacterium or antigen as taught by Muller et al or 1999 or Drancourt 1999 in a routinely used immunoassay method for detecting antibodies as taught by Harlow and Lane because *Tropheryma whippelii* bacterium or antigen and the methodology for detecting the antibody are taught by these two prior arts. The claimed invention is prima facie obvious over Muller et al or 1999 or Drancourt 1999 in view of Harlow and Lane absent any convincing evidence to the contrary.

Applicants' arguments filed on 9/9/05 has been fully considered but they are not deemed to be persuasive.

Applicant states that the prior art Tropheryma *whippelii* culture cannot be used as a basis for establishing the bacterium in culture in such a way that it can be multiplied because the mean lifetime of monocytes is only 30 days, which is insufficient in view of the doubling time of the bacterium. In particular, since human blood monocytes do not multiply, the primary culture described in Schoedon and Muller cannot be used as a

basis for multiplication of the bacterium. Applicant provided the Declaration by Prof Drancourt who was one of the authors in the prior art reference cited by the examiner.

The examiner does not agree with the applicant because Schoedon and Muller disclose *T.Whippelii* replicate in IL4 treated monocytic U937 as well as SigM5 cell lines. These cell lines grow continuously in cell culture as SigM5 and U937 as these are well established immortalized cell lines that can grow continuously. Additionally, it appears that simple growth medium is sufficient for these bacteria to grow continuously. Both the references indicate that primary human monocytes have been used to isolate the bacteria from tissue samples and later expanded in cell lines using simple growth medium.

The examiner does not agree with the applicant because the art discloses *T.Whippelii* is propagated in SigM5 or U937 cell line after the bacterium is isolated from IL4 treated monocytes. This cell line grows continuously in culture as SigM5 is an immortalized cell line and it is not primary human monocyte as stated by the applicant. Further, method of detecting antigen or antibody is routinely used as taught by Harlow and Lane.

The examiner acknowledges the Declaration provided by Prof Drancourt. However the Declaration fails to provide the evidence that *Tropheryma whippelii* could not be cultivable in cell lines U937 and SigM5. Further, the Declaration does not indicate what are the specific characteristics of the claimed culture over the prior art culture. Further, the declaration or the claims do not indicate how the bacterium reproducibly multiplied for two months or over in fibroblast cell line. The declaration does not provide the differences between prior art culture and the claimed culture. Further, the letter from Schoedon clearly indicates that Whipple's disease is rare in Switzerland and especially supply of material from additional patients would be very

limited. Hence the requested isolate was no longer available to supply due to funding problems. However, Schoedon's letter does not indicate that *T.Whippelii* cannot be grown in culture. Additionally, Relman (1997, JID176: 752-754) acknowledges Schoedon's key contribution to clinical microbiology by isolating and culturing *Tropheryma whippelii.*

Applicant stated that none of these isolates have been deposited and therefore, they do not exist.

The examiner disagrees with the applicant because many bacterial and viral isolates from various clinical samples are routinely being isolated in several labs and yet may not be deposited. However, it appears that the applicant has isolated the bacterium *T.Whippelii* from a *different* source and deposited the bacterial culture under CNCM I-2202 and the hybridoma cell line CNCM I-2411 that produces antibodies and recognize *T.Whippelii* CNCM I-2202 and thus this isolate can be distinguished from the prior art isolates. Therefore, it is very important to amend the claims to recite the characteristics of culture *T.Whippelii* CNCM I-2202 that is grown in fibroblast and the monoclonal antibody obtained from hybridoma cell CNCM I-2411 that specifically recognized said *T.Whippelii* CNCM I-2202 to overcome the rejection.

Remarks

7. Claims 3, 10, 32 and 33 are objected as they depend on rejected base claim 1.

Claims 1, 4-5, 11, 15, 25, 29 and 30-31 are rejected.

Relevant Prior Art

8. The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

Relman 1997(J.I.D. 176: 752-754).

Relman's teachings indicate T.Whippelii *is* isolated and cultured. He states that no microorganism is uncultivable when one understands the intimate growth requirements of the bacteria.

Pace et al, U.S.Patent 6,083,683

Pace et al teach a method or in a diagnostic immunoassay kit for the diagnosis of infection (Shigella) in a biological sample (i.e., serum or any other biological fluid) comprising contacting said biological sample with a bacterium or antigen or a fragment thereof having an enhanced antigenic property wherein said bacterium is harvested from a culture and detecting an antibody present in said biological sample binding to the *Shigella* bacterium or fragment thereof wherein said detecting is by means of an immunoassay ,wherein said immunoassay is a radioimmunoassay, enzyme-linked immunosorbent assay (ELISA,), fluorescent immunoassay, or fluorescence polarization immunoassay (FPIA). The immunoassay or a diagnostic immunoassay used micro titer plates (solid support) for binding bacteria or antigen, and a conjugate antibody. Thus, the art teaches immunoassays for diagnosing bacterial disease associated with bacteria using either bacterium or antigen of said bacterium.

Conclusion

9. **THIS ACTION IS MADE FINAL**. See MPEP ' 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such

papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Please note: The applicant requested the examiner for an interview 9see 11/21/05 interview summary with the examiner) and the examiner would inform the applicant after scheduling an interview with Technology Quality Specialist.

Padma Baskar Ph.D.

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600